REMARKS

I. Pending Claims

Claims 1-20 are currently pending in the instant application. Claims 14-16 are under active consideration. Claim 14 has been amended, and claims 1-13 and 17-20 have been withdrawn from consideration. Claims 21-57 have been canceled. Applicants expressly do not disclaim the subject matter of any invention disclosed herein which is not set forth in the instantly filed claims. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications.

II. Support for the Amendments

Claims 14 and 16 have been amended to incorporate the limitations of non-elected claim 12, from which they had depended. Support for this amendment may be found in original claims 3, 4, 5, 6, 7 and 8, as well as in the Specification at page 14, line 27 through page 15, line 9. No new matter is added by this amendment. It is believed that the claims, as amended, recite patentable subject matter.

III. Restriction requirement/election

It is noted that election, with traverse, of the claims of Group IV (encompassing claims 14-16), drawn to a method of detecting a target polynucleotide encoding a methyltransferase protein, has been acknowledged by the Examiner.

IV. Priority

In response to the Examiner's request, Applicants have amended the Specification to reflect the fact that U.S. Application Serial No. 09/149,534 issued as U.S. Patent No. 6,379,722 on April 30, 2002.

V. Information Disclosure Statement

The Examiner has stated that the listing of references in the Specification is not a proper information disclosure statement (Office Action mailed May 16, 2003; page 4).

Applicants note that the Examiner acknowledged Applicants' information disclosure statement filed on December 18, 2001, and considered all the references listed on May 14, 2003.

VI. Claim Objections

The Examiner has objected to claims 14-16 as being dependent upon non-elected claim 12. Applicants have amended claim 14 to incorporate all limitations of claim 12.

Withdrawal of this objection is therefore respectfully requested.

VII. Indefiniteness rejection under 35 U.S.C. § 112, second paragraph

Claims 14 and 15 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner has stated that claim 14 (and 15, dependent therefrom) is indefinite since the phrase "specifically hybridizes" is allegedly not defined in the specification (Office Action mailed May 16, 2003; page 5). Applicants respectfully disagree and traverse the rejection.

A. The claims must be examined on the basis of whether one having ordinary skill in the art would be able to determine the scope of the claim

One of skill in the art would readily be able to determine the meaning of the term "specifically hybridizes." The M.P.E.P. provides guidelines to Examiners for rejections under 35 U.S.C. § 112, second paragraph as follows:

> ...a full explanation of the deficiency of the claims should be supplied. Whenever possible, identify the particular term(s) or limitation(s) which render the claim(s) indefinite and state why such term or limitation renders the claim indefinite. If the scope of the claimed subject matter can be determined by one having ordinary skill in the art,

a rejection using this form paragraph would not be appropriate (M.P.E.P. § 706.03(d)).

Therefore, claims must be examined on the basis of whether one having ordinary skill in the art would be able to determine the scope of the claim and, if a rejection is made, reasons must be provided why the claim is indefinite. Applicants submit that the Examiner has not provided any reasons or evidence why the cited phrase is indefinite and/or why one having ordinary skill in the art could not determine the scope of the claim. For this reason alone, the rejection is improper and should be withdrawn.

B. The term "specifically hybridizes" is well-understood in the art

Applicants submit that "specifically hybridizes" has the plain meaning of the words, and that the skilled artisan would understand that "specifically hybridizes" is the complementary base pairing of the nucleotide sequences encompassed by the claims. As a general rule, claim language carries the ordinary and accustomed meaning of the words in their normal usage in the field of invention (Toro Co. v. White Consol. Indus., 199 F.3d 1295, 53 USPQ2d 1065, 1067 Fed. Cir. 1999). The dictionary defines "specific" as "restricted to a particular individual, situation, relation, or effect." (Attachment No. 1; Merriam-Webster's Collegiate Dictionary; Merriam- Webster OnLine: http://www.m-w.com). Hence, the phrase "specifically hybridizes" indicates that the probes of claims 14-16 bind only to the polynucleotides of claim 12 and thus would not by definition bind to simply any oligomer. It is well known and an inherent requirement of the method that the primers used in PCR amplification must specifically hybridize to the target polynucleotide.

Furthermore, the use of the term "specifically hybridizes" distinguishes a sequence that base pairs with its complement above background "noise," from those sequences that do not. The Specification describes how to remove such "nonspecific signals" see e.g., Example VI. Hybridization is the association of two complementary nucleic acid strands to form double-stranded molecules, which can contain two DNA strands, two RNA strands, or one DNA and one RNA strand. Hybridization is

sed experimentally in various ways to detect specific DNA or RNA sequences" (Attachment No. 2; Lodish, Harvey F. 1986 Molecular Cell Biology. Fourth Edition W. H. FREEMAN).

Applicants also call the Examiner's attention to M.P.E.P § 2111.01, which states that "[p]lain meaning refers to the meaning given to the term by those of ordinary skill in the art."

Thus, one of skill in the art would understand the meaning of the term "specifically hybridizes" within the context of the claims.

C. The Specification contains adequate support for the meaning of the term, "specifically hybridizes"

There is adequate definition of the term "specifically hybridizes" in the Specification. An inventor may act as his own lexicographer and use the specification to supply new meanings for terms implicitly or explicitly (Markman v. Westview Instruments, Inc., 52 F.3d 967, 979-80, 34 USPQ2d 1321, 1330 (Fed. Cir. 1995) en banc, aff'd 517 U.S. 370 (1996)).

In Example VI (page 48, line 22; through page 49, line 7) in the Specification describes how to label and use individual DNA probes for hybridization. The protocol in Example VI suggests the optimal length for the probes, how to purify the probes after labeling, and how to remove nonspecific signals. The Specification also defines the term "hybridization" on page 10, lines 20-21. The terms "complementary" and "complementarity" are defined as referring to the "natural binding of polynucleotides under permissive salt and temperature conditions by base-pairing," see page 8 at lines 20-28 as well as page 9, line 28 through page 10, line 12 (definition of homology, and description of conditions of low and high stringency). The terms "stringent conditions" and "stringency" are defined on page 12, lines 15-26 of the Specification. The Specification provides,

> "The terms 'stringent conditions' or 'stringency', as used herein, refer to the conditions for hybridization as defined by the nucleic acid, salt and temperature. These conditions are well known in the art and may be altered in order to identify or detect identical or related polynucleotide sequences. Numerous equivalent conditions comprising either low or high stringency depend on factors such as the length and nature of the sequence (DNA, RNA, base composition), nature of the target (DNA, RNA, base composition), milieu (in solution or immobilized on a solid substrate), concentration of salts and other components (e.g., formamide, dextran sulfate and/or polyethylene glycol), and temperature of the reactions (within a range from about 5°C below the melting

temperature of the probe to about 20°C to 25°C below the melting temperature). One or more factors be may be varied to generate conditions of either low or high stringency different from, but equivalent to, the above listed conditions."

The foregoing paragraph clearly outlines the parameters that allow one of skill in the art to attain specific hybridization of single polynucleotide strands. Because exact formulas for reassociation of single strands differ depending on factors such as length and nature of the sequence, target, and milieu, a general teaching was provided for those skilled in the art. Applicants submit that these conditions are well known in the art and may be altered by the skilled artisan depending on specific objectives.

Further, on page 37, lines 1-8, of the Specification, Applicants describe the specificity of probes used to identify naturally occurring sequences encoding SAM-MT, or related sequences. In addition, on page 37, lines 14-21 of the Specification, Applicants describe means for producing specific hybridization probes for DNAs encoding SAM-MT. The Specification also discusses the length and nature of oligonucleotides to be used in microarray experimentation on page 40, lines 16-27 of the Application.

D. The probes of claim 14 are adequately defined by the claim, the Specification, and what is known to one of skill in the art

The Examiner has stated that "[t]here is nothing to suggest 'which probes' 'specifically hybridize' to said target polynucleotide(s)..." (Office Action mailed May 16, 2003; page 5). Applicants submit that the probes of claim 14 are adequately defined by the claim, the Specification; e.g., the sequence of SEQ ID NO:2 as listed in the Sequence Listing, and what is known to one of skill in the art.

VII. Written description rejection under 35 U.S.C. § 112, first paragraph

Claims 14-16 stand rejected under 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. This rejection is respectfully traversed.

A. No description of the function of the polynucleotides is required to satisfy the written description requirement for the claimed methods of detecting the target polynucleotides

The written description requirement does not require Applicants to disclose the function of the polynucleotides referenced in the claimed methods of detecting the claimed polynucleotides and fragments thereof. The Examiner states that claims 14-16 are rejected because "[t]here is no disclosure of any particular structure to function/activity relationship in the single disclosed target polynucleotide (i.e., SEQ ID NO:2)" (Office Action mailed May 16, 2003; page 6). The Examiner further alleges that "[t]he specification also fails to describe additional representative species of target polynucleotides and thus the claimed methods" (Office Action mailed May 16, 2003; page 6).

In the Office Action, the Examiner attempts to introduce a "functional limitation" to the target polynucleotides of the claims, limitations which are not present in claims 14-16.

Applicants respectfully remind the Examiner that disclosure of functional characteristics is merely one of the factors which can be used as evidence that Applicants were in possession of the claimed invention at the time of filing. In addition, functional limitations are not necessary as the structural and source limitations are sufficient to describe the target polynucleotides of the claims and in any case, "biological function" is irrelevant to the use of the claimed methods and target polynucleotides of the claims in toxicology testing (Infra. Section VIII).

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are also well-established by case law:

> ...the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed* (Vas-Cath, Inc. v. Mahurkar, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) (emphasis added)).

The Examiner's position is clearly contrary to the USPTO's own written description guidelines ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, para. 1", published January 5, 2001), which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met (footnotes omitted; emphasis added).

B. The specification provides an adequate written description of the structure of the target polynucleotides of the claims

The subject matter encompassed by claims 14-16 is either disclosed by the Specification or is conventional or well known to one skilled in the art.

SEQ ID NO:1 and SEQ ID NO:2 are specifically disclosed in the Specification (see, for example, the Sequence Listing at pages 54-56). Variants of SEQ ID NO:1 and SEQ ID NO:2 are described, e.g., at page 3, lines 14-15, page 13, lines 13-21, page 14, lines 25-29, page 15, lines 5-12, and page 37, lines 1-10. Incyte clones in which the nucleic acids encoding the human SAM-MT were first identified and libraries from which those clones were isolated are described, for example, at page 13, line 28 through page 14, line 4 of the Specification. Chemical and structural features of SEQ ID NO:1 are described, for example, at page 14, lines 5-19. The Specification describes (e.g., page 45, lines 1-21) how to use BLAST to determine whether a given sequence falls within the "at least 90% identical" scope. Complementary sequences are described, e.g., at page 8, lines 6-9, page 8, lines 20-28, page 11, lines 10-12, and page 49, lines 12-21. RNA equivalents are described, e.g., at page 11, lines 10-12 and page 36, lines 26-27.

One of ordinary skill in the art would recognize the target polynucleotides of the claims. Given SEQ ID NO:2, one of ordinary skill in the art would recognize a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID

NO:2. Accordingly, the specification provides an adequate written description of the structure of the claimed genus of polynucleotides, upon which the claimed methods are based.

There is simply no requirement that the claims recite, for example, particular variant polynucleotide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polynucleotide variants are defined in terms of SEQ ID NO:2 ("...a polynucleotide comprising...a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:2"). Because the claimed polynucleotide variants, as well as the claimed complementary sequences and RNA equivalents, are defined in terms of SEQ ID NO:2, the precise chemical structure of every target polynucleotide within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Applicants to unduly limit the scope of their claimed invention.

The Examiner also states that claims 14-16 "are directed to **all** possible methods for detecting **any** target polynucleotide of claim 12" (Office Action mailed May 16, 2003; page 5; emphasis added). To the contrary. The Examiner has misinterpreted Applicants' claims. Applicants' claims are restricted to the detection of polynucleotides from five specific groups: "a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:2, b) a polynucleotide comprising a naturally occurring polynucleotide at least 90% identical to a polynucleotide sequence of SEQ ID NO:2, c) a polynucleotide complementary to a polynucleotide of a), d) a polynucleotide complementary to a polynucleotide of b), and e) an RNA equivalent of a)-d). Thus, only those sequences that share 90% sequence identity with SEQ ID NO:2 are claimed; certainly many others could be detected. Moreover, Applicants have further limited the claims to the detection of "naturally occurring" variants of SEQ ID NO:2.

The Specification at page 6, lines 3-6, defines "SAM-MT" as "the amino acid sequences of substantially purified SAM-MT obtained from any species, particularly mammalian, including bovine, ovine, porcine, murine, equine, and preferably human, from any source whether natural, synthetic, semi-synthetic, or recombinant." Hence, it is apparent that the inventors contemplated naturally occurring variants of SEQ ID NO:1.

The term "naturally occurring" is a well-known term in the art which Applicants intended to be used in such context. As such, no further definition of the term is necessary (MPEP 2163 IIA3(a)):

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

One of ordinary skill in the art would recognize that "***a naturally occurring polynucleotide sequence***" as recited in claim 14 is one which occurs in nature. Through the process of natural selection, nature will have determined the appropriate nucleic acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of SAM-MT) and SEQ ID NO:2 (the polynucleotide sequence encoding SAM-MT), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application.

C. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to methods of detecting specific polynucleotides) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human

fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define methods of detecting polynucleotides in terms of chemical structure, rather than functional characteristics. For example, the language of independent claim 14, as amended, recites chemical structure to define the claimed genus:

> 14. A method for detecting a target polynucleotide in a sample, said target polynucleotide selected from the group consisting of:
> a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:2,
> b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:2,
> c) a polynucleotide complementary to a polynucleotide of a),
> d) a polynucleotide complementary to a polynucleotide of b), and
> e) an RNA equivalent of a)-d); the method comprising:
> i) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and
> ii) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:2. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claims. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

D. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope. In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; Attachment No. 3). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that >40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to polynucleotides encoding polypeptides related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as SAM-MT proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polynucleotides comprising "a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2." This variation is far less than that of all potential SAM-MT proteins related to SEQ ID NO:1; i.e., those SAM-MT proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

E. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an

Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of July 25, 1997. Much has happened in the development of recombinant DNA technology in the 17 years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the target polynucleotides of the claims at the time of filing of this application.

F. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Office Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above. Applicants have provided an adequate written description of the claimed methods of detecting the target polynucleotides and fragments thereof.

Accordingly, this rejection should be withdrawn.

VIII. Enablement rejection under 35 U.S.C. § 112, first paragraph

Claims 14-16 have been rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use the claimed methods of detecting the recited polynucleotides and fragments thereof. In particular, the Examiner has asserted that the specification "while being enabling for the claimed hybridization and amplification methods of detection of a target polynucleotide, using a polynucleotide consisting of SEQ ID NO:2 and fragments thereof as a hybridization probe or an amplification primer, wherein the target polynucleotide comprises SEQ ID NO:2 which encodes a methyltransferase, does not reasonably provide enablement for any hybridization or amplification method of detection of a target polynucleotide, using any polynucleotide comprising at least 20 contiguous nucleotides complementary to said target polynucleotide as a hybridization probe or any amplification primer, where in the target polynucleotide comprises a naturally occurring sequence at least 90% identical to SEQ ID NO:2" (Office Action, May 16, 2003; paragraph bridging pages 6 and 7). Such, however, is not the case.

The first paragraph of 35 U.S.C. §112 requires that the specification describe how to make and use the claimed subject matter. As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

The foregoing indicates that there is no requirement under the law to provide "working examples" of what is claimed. Rather, one looks to the Specification for a description of how to make and use what is claimed.

Applicants submit that the present Specification contains the requisite description, and provides ample teaching of the manner and process for making and using the invention.

A. How to make

The Specification provides sufficient teaching of the manner and process of *making* the invention. The Office Action alleges that "[b]ecause of the lack of guidance, the extended experimentation that would be required to determine how to make many of the required hybridization probes and primers and how to use most of the detected target polynucleotides it *[sic]* would require undue experimentation for one skilled in the art to arrive at the claimed methods." (Office Action mailed May 16, 2003; page 8).

SEQ ID NO:1 and SEQ ID NO:2 are specifically disclosed in the Specification (see, for example, the Sequence Listing at pages 54-56). Variants of SEQ ID NO:1 and SEQ ID NO:2 are described, e.g., at page 3, lines 14-15, page 13, lines 13-21, page 14, lines 25-29, page 15, lines 5-12, and page 37, lines 1-10. Incyte clones in which the nucleic acids encoding the human SAM-MT were first identified and libraries from which those clones were isolated are described, for example, at page 13, line 28 through page 14, line 4 of the Specification. Chemical and structural features of SEQ ID NO:1 are described, for example, at page 14, lines 5-19. "Naturally occurring" polynucleotide sequences occur in nature; they are not created exclusively in a laboratory. The Specification describes how to find naturally occurring homologs in other individuals and species (e.g., page 37, lines 1-3) and how to use CLUSTAL V and BLAST to determine whether a given naturally occurring polynucleotide sequence falls within the "at least 90% identical to a polynucleotide sequence of SEQ ID NO:2" scope (e.g., page 45, lines 1-21).

The making of the target polynucleotides of the claims by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 18, lines 27-30, page 19, line 13 through page 24, line 14, and page 31, lines 22-29. The making of the probes of the claims is disclosed in the Specification, e.g, at page 24, line 24 through page 25, line 7, page 37, lines 1-21, page 39, lines 20-27, page 40, line 16 through page 42, line 3, page 48, lines 23-33, and page 49, lines 9-30. This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

B. How to use

Applicants' invention is directed, *inter alia*, to methods of detecting polynucleotides encoding polypeptides having homology to Caenorhabditis elegans putative methyltransferase (GI 1065505).

The claimed methods and target polynucleotides have a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of SEQ ID NO:1 (SAM-MT), for toxicology testing, and for drug discovery (see the Bandman '933 Specification at, e.g., page 36, line 25 through page 42, line 3). As described in the Specification:

> Nucleic acids encoding the SAM-MT of the present invention were first identified in Incyte Clone 10625 from the THP-1 promonocyte cell line, PMA+LPS stimulated, cDNA library (THP1PLB01) using a computer search for amino acid sequence alignments. A consensus sequence, SEQ ID NO:2, was derived from the following overlapping and/or extended nucleic acid sequences: Incyte Clones 10625 (THP1PLB01), 1749286 (STOMTUT02), 1689223 (PROSTUT10), 075978 (THP1PEB01), and 2731022 (OVARTUT04).
>
> In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:1, as shown in Figs. 1A, 1B, and 1C. SAM-MT is 281 amino acids in length, with a predicted relative molecular mass of 31.9 kDa (MacDNASIS PRO software). SAM-MT has three potential protein kinase C phosphorylation sites at residues S-194, S-240, and T-273, and one potential tyrosine kinase phosphorylation site at residue Y-48. As shown in Figs. 2A and 2B, SAM-MT has chemical and structural homology with the putative methyltransferases from C. elegans (GI 1065505; SEQ ID NO:3) and S. cerevisiae (GI 1907189; SEQ ID NO:4). In particular, SAM-MT and C. elegans putative methyltransferase share 51% amino acid sequence identity, share the AdoMet-MT motifs I and III, and share one protein kinase C phosphorylation site. As illustrated by Figs. 3A and 3B, SAM-MT and C. elegans putative methyltransferase have rather similar hydrophobicity plots.
>
> As shown in Figs. 4A and 4B, SAM-MT contains three common consensus sequence motifs of the small molecule methyltransferase enzymes (AdoMet-MT) that utilize AdoMet as a substrate or product.
>
> Northern analysis shows the expression of this sequence shows expression in various libraries, at least 60% of which are immortalized or cancerous, 50% are from secretory tissue, and at least 41% of which involve immune response. Of particular note is the expression of SAM-MT in gut, reproductive, and neural tissue; in proliferating cells; in fetal lung, gut, and heart; and in placenta.
>
> (See the '933 Bandman Specification at page 13, line 28 through page 14, line 19).

Claims 14-16 stand rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the use of the claimed methods is not adequately enabled. The rejection alleges in particular that "the specification...does not reasonably provide enablement for any hybridization or amplification method of detection of a target polynucleotide, using any polynucleotide comprising at least 20 contiguous nucleotides complementary to said target polynucleotide as a hybridization probe or any amplification primer, wherein the target polynucleotide comprises a naturally occurring sequence at least 90% identical to SEQ ID NO:2" (Office Action mailed May 16, 2003; pages 6-7).

The rejection of claims 14-16 is improper, as the invention of those claims is enabled with respect to one of ordinary skill in the art.

The invention at issue includes methods for detecting polynucleotide sequences corresponding to a gene that is expressed in a PMA + LPS stimulated human THP-1 promonocyte cell line. The SEQ ID NO:2 polynucleotide codes for a polypeptide demonstrated in the patent specification to be a member of the S-adenosylmethionine methyltransferase (AdoMet-MT) family of proteins, whose biological functions include catalyzing the transfer of methyl groups from S-adenosylmethionine to acceptor molecules such as phosphotidylethanolamine or the polynucleotide 5' cap of viral mRNA (Bandman '565 application, pages 1-2.) As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the polynucleotide detected by the claimed methods actually functions.

Applicants submit with this response the declaration of Tod Bedilion[1] describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the enablement of the claimed methods are without merit.

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[1]The Bedilion Declaration is filed herewith in unexecuted form. The executed Declaration will be filed as soon as it is available.

The Bedilion declaration describes, in particular, how the claimed methods of detecting expressed polynucleotides can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the SEQ ID NO:2 detected by the claimed methods is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would appreciate that cDNA microarrays that contained the target polynucleotides, or fragments thereof, would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating neoplastic, immunological, and vesicle trafficking disorders for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration ¶ 15.)

The Patent Examiner contends that the claimed methods of detecting the SEQ ID NO:2 variant polynucleotides cannot be useful without precise knowledge of the biological function of the SEQ ID NO:2 variant polynucleotides. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed methods and the SEQ ID NO:2 polynucleotide detected by the claimed methods in the absence of any knowledge as to the precise function of the polypeptide encoded by the SEQ ID NO:2 polynucleotide. The uses of the claimed methods in gene expression monitoring applications are in fact independent of the precise function of the polypeptide encoded by the SEQ ID NO:2 polynucleotide.

Under the circumstances, Applicants are submitting with this response a Declaration of Dr. Tod Bedilion under 37 C.F.R. § 1.132 (the Bedilion Declaration). As we will show, the Bedilion Declaration and these further references shows the many substantial reasons why the Examiner's new positions and arguments, in particular with respect to the use of the claimed methods and the SEQ ID NO:2 polynucleotide detected by this method e.g., in a cDNA microarray, are without merit, and that the ignored toxicology disclosure should have been given additional and more adequate consideration.

1. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").
> *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

2. Uses of the claimed methods for diagnosis of conditions and disorders characterized by expression of SAM-MT for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

a. The use of the claimed methods and the SEQ ID NO:2 variant polynucleotides detected by those methods for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. The claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed methods and the SEQ ID NO:2 variant polynucleotides detected by those methods.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the parent Bandman '565 application on July 25, 1997 would have understood that application to disclose the claimed methods and the SEQ ID NO:2 variant polynucleotides detected by those methods to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of those specific polynucleotides in connection with the development of drugs and the monitoring of the activity of such drugs. (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed methods and the SEQ ID NO:2 variant polynucleotides detected by those methods in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications. (Bedilion Declaration, ¶¶ 12 and 15).[2]

In connection with his explanations, Dr. Bedilion states that the "Bandman '565 application would have led a person skilled in the art on July 25, 1997 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of neoplastic, immunological, and vesicle trafficking disorders to conclude that a cDNA microarray that contained the target

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[2]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Bandman '565 specification, that the claimed methods and the SEQ ID NO:2 variant polynucleotides detected by those methods would be useful in connection with developing new drugs using technology, such as northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

polynucleotides or fragments thereof would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the target polynucleotides, or fragments thereof" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would appreciate that cDNA microarrays that contained the target polynucleotides, or fragments thereof, would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating neoplastic, immunological, and vesicle trafficking disorders for such purposes as evaluating their efficacy and toxicity" *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-July 25, 1997 publications showing the state of the art on July 25, 1997. (Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include over four pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on July 25, 1997 (and for several years prior to July 25, 1997) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be considered and evaluated in connection with the development of the drug" and how the teachings of the Bandman '565 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Bandman '565 application at the time it was filed "would have would have wanted their cDNA microarray to have a probe...to any of the target polynucleotides because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to July 25, 1997" (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Bandman '565 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed methods and the target polynucleotides and fragments thereof, detected by that method.

Nowhere does the Patent Examiner address the fact that, as described on pages 36, line 25 through page 42, line 3 and page 49, lines 9-30 of the Bandman '933 application, the SEQ ID NO:2 variant polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the SEQ ID NO:2 variant polynucleotides. The SEQ ID NO:2 variant polynucleotides detected by the claimed methods are not, in that regard, random sequences whose value as probes is speculative or would require further research to determine.

Given the fact that the target polynucleotides and fragments thereof detected by the claimed methods are known to be expressed, their utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., they are useful in analyzing compounds)" (emphasis added)).

The Bedilion Declaration shows that a number of pre-July 25, 1997 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Bandman '565 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Exhibits A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Exhibit D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including

> "monitoring of gene expression" applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

A literature review published after the filing of the Bandman '565 application describing the state of the art further confirms the claimed invention's utility. Rockett, et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up– or down-regulated is required.
>
> * * *
>
> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination (emphasis in original).

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, Xenobiotica 29:655-691 (1999) (Attachment No. 4)

In an article published shortly after the filing of the Bandman '565 application, Lashkari, et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay. (Attachment No. 5, page 8945, emphasis added)

Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947 (Attachment No. 5).

b. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Bedilion in his declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al. (Attachment No. 4), *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs (Attachment No. 4, page 656).

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Attachment No. 6); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000) (Attachment No. 7).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip. (Attachment No. 6, page 156.)

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999) (Attachment No. 8, see page 683). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Attachment No. 9), indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be withdrawn regardless of their merit.

c. The similarity of the polypeptides encoded by the SEQ ID NO:2 variant polynucleotides to another polypeptide of undisputed utility demonstrates utility and enablement for the claimed methods

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, the utility and enablement of the claimed methods and target polynucleotides and fragments thereof detected by those methods can be imputed based on the relationship between the

polypeptide encoded by the detected SEQ ID NO:2 variant polynucleotides, and another polynucleotide of unquestioned utility, the SEQ ID NO:1 polypeptide SAM-MT.

The polypeptides have sufficient similarities in their sequences that a person of ordinary skill in the art would recognize more than a reasonable possibility that the polypeptide encoded by the SEQ ID NO:2 polynucleotide variants have utility similar to the SEQ ID NO:1 polypeptide. Applicants need not show any more to demonstrate utility. In re Brana, 51 F.3d at 1567.

It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., (Attachment No. 3).

The Examiner must accept the Applicants' demonstration that the homology between the SEQ ID NO:2 variant polynucleotides and the SEQ ID NO:2 polynucleotide demonstrates utility and enablement by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility and enablement. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

d. Objective evidence corroborates the utilities and enablement of the claimed invention

There is, in fact, no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing the sequences of all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is

independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed methods and polynucleotides detected by that method and its use of those polynucleotides on cDNA microarrays, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

3. The Patent Examiner's rejections are without merit

Rather than responding to the evidence demonstrating utility and enablement of the methods claimed, the Examiner attempts to dismiss this altogether by arguing that the disclosed and well-established uses for the claimed methods and target polynucleotides are not enabled (Office Action mailed May 16, 2003; pages 6-8). The Examiner is incorrect both as a matter of law and as a matter of fact.

a. The precise biological role, function, or activity of an expressed polynucleotide is not required to demonstrate utility and enablement

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise biological "activity" of the SEQ ID NO:2 variant polynucleotides detected by the claimed methods, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the SEQ ID NO:2 variant polynucleotides detected by the claimed methods either by themselves

or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function, role, or activity of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any nucleic acid detected by the claimed methods, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility and enablement. Rather than looking to the biological function, role, or activity of the SEQ ID NO:2 variant polynucleotides detected by the claimed methods, the Examiner

should have looked first to the benefits the SEQ ID NO:2 variant polynucleotides and the claimed methods are alleged to provide.

b. Membership in a class of useful products can be proof of utility and enablement

Despite the uncontradicted evidence that the claimed methods detect a polynucleotide encoding polypeptides in the S-adenosylmethionine methyltransferase family, and the family of expressed polypeptides, the Examiner refused to impute the utility of the members of the S-adenosylmethionine methyltransferase protein family to the polypeptides encoded by the SEQ ID NO:2 variant polynucleotides.

In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses the polypeptide encoded by the SEQ ID NO:2 variant polynucleotides as if the general classes in which they are included are not the S-adenosylmethionine methyltransferase protein family, and the family of expressed polypeptides, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may

contain a substantial number of useless members, the S-adenosylmethionine methyltransferase protein family and the family of expressed polypeptides do not. The S-adenosylmethionine methyltransferase protein family and the family of expressed polypeptides are sufficiently specific to rule out any reasonable possibility that the polypeptides encoded by the SEQ ID NO:2 variant polynucleotides would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the family of S-adenosylmethionine methyltransferase proteins, and the family of expressed polypeptides have any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the polypeptides encoded by the SEQ ID NO:2 variant polynucleotides detected by the claimed methods are useful. It follows that the claimed methods and the SEQ ID NO:2 variant polynucleotide detected by the claimed methods also are useful.

c. Because the uses of the claimed methods and SEQ ID NO:2 variant polynucleotides in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has adequate utility and enablement

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the detected SEQ ID NO:2 variant polynucleotides or their protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the detected SEQ ID NO:2 variant polynucleotides or their protein products themselves, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include the use of the claimed methods in chromosomal mapping (Bandman '933 application, page 42, line 4, through page 43, line 3).

IX. Claim Rejections – 35 U.S.C. § 103

Claims 14-16 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Boker et al. (Journal of Biological Chemistry, Vol. 269, No. 26, pages 17697-17704, 1994, and Hillier et al. (Wash-Merck EST Project, GENBANK Accession Number AA054310, December 1996). The Examiner alleges that one of ordinary skill in the art would have been motivated to use the nucleotide sequence disclosed by Hillier et al. to detect and isolate a full length methyltransferase cDNA clone, in view of the teachings of Boker et al., thus rendering the instant invention obvious. Applicants respectfully traverse.

Hillier et al. disclose a 463 nucleotide human cDNA fragment. SEQ ID NO:2 is 672 nucleotides longer than the Hillier fragment. The Hillier et al. reference does not disclose that the cited AA054310 fragment encodes a methyltransferase. In addition, the Bokar et al. reference does not disclose any sequence.

Applicants respectfully submit that the Examiner has mischaracterized Applicants' claims, and continues to fail to give proper consideration to the entire claims in making the rejection.

Applicants' rejected claims are as follows:

14. A method for detecting a target polynucleotide in a sample, said target polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:2,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d); the method comprising:

i) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

ii) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

15. A method of claim 14, wherein the probe comprises at least 60 contiguous nucleotides.

16. A method for detecting a target polynucleotide in a sample, said target polynucleotide selected from the group consisting of::

a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:2,
b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:2,
c) a polynucleotide complementary to a polynucleotide of a),
d) a polynucleotide complementary to a polynucleotide of b), and
e) an RNA equivalent of a)-d); the method comprising; the method comprising:

i) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and
ii) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

Applicants note that in all three of the claims, drawn to methods of detecting specific polynucleotides, the preamble to the claim contains the implicit limitation "said target polynucleotide having a sequence of a polynucleotide of claim 12," as in claims 14-16 (which were amended to incorporate all of the limitations of claim 12). In this case, the preamble "breathes life and meaning" into the claim and thus is a limitation which is **not** taught by the prior art. Moreover, it should be noted that the product of these methods is a complex or other product necessarily defined by the novel sequences of claims 14-16, as currently amended.

A. The Examiner has mischaracterized the claims

First and foremost, this rejection is inappropriate because the Examiner has failed to cite any references which, either alone or in combination, would render obvious the claimed methods, which relate to methods of detecting a specific, particular sequence.

Applicants do not claim a method for detecting all polynucleotides encoding methyltransferases. Applicants claim a method for detecting **the** polynucleotides of claim 12, which are referred to in claims 14-16, as currently amended. The Examiner continues to improperly construe the claim language by failing to give weight to the limitation of the preamble, "said target polynucleotide having a sequence of a polynucleotide of claim 12."

As was discussed in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 51 USPQ2d 1161 (Fed. Cir 1999):

> If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is "necessary to give life, meaning, and vitality" to the claim, then the claim preamble should be construed as if in the balance of the claim. *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 480-81 (CCPA 1951); see also, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997); *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257, 9 USPQ2d 1962, 1966 (Fed. Cir. 1989). Indeed, when discussing the "claim" in such a circumstance, there is no meaningful distinction to be drawn between the claim preamble and the rest of the claim, for only together do they comprise the "claim".

Thus, it is clear that the Examiner cannot disregard the limitation recited in the preamble, i.e., that the product detected is a specific sequence, and that sequence is not only novel, it is unobvious itself . Yet, this is what the Examiner has done. Applicants have already received a patent on SEQ ID NO:2. Therefore, it is free from prior art.

To constitute an obviousness rejection under 35 U.S.C. 103(a), the cited reference must teach each and every limitation of the claimed invention. Hillier et al. does not teach SEQ ID NO:2. Accordingly, the combined cited prior art does not teach or suggest each and every limitation of claims 14-16. When claims 14-16 are properly construed, they are not obvious under 35 U.S.C. 103(a).

B. Failure to establish a prima facie case of obviousness

The Examiner has asserted that, one of ordinary skill in the art would have been motivated to use the polynucleotide of Hillier et al., "to detect an isolate a full length human methyltransferase cDNA clone, to lead to a better understanding of the underlying complexity of the methylation of nucleic acids as a post-transcriptional modification mechanism" (Office Action of May 16, 2003; page 10). Applicants respectfully traverse this rejection on the ground that the Examiner has clearly failed to establish a proper *prima facie* case of obviousness.

1. Hindsight reconstruction

The nucleic acid sequence of SEQ ID NO:2 and the corresponding the full-length sequence of the human S-adenosyl-L-methionine methyltransferase gene was not known until Applicants elucidated it.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. The rejection focuses on the probes used in the claimed methods, and asserts that the Hillier et al. document makes obvious the identity of particular probes which could be used to practice the recited methods of detection. Following this logic, the Examiner concludes that the methods are obvious because the probes are obvious. It may be possible that such logic would apply if the recited methods were directed to detecting **any** target polynucleotide which hybridizes to probes generated from the sequence of Hillier et al. However, this is not the case with the recited methods of detection. The claims in question recite methods of detecting specific target polynucleotides which are disclosed in the specification. For example, claim 14, as currently amended, implicitly recites a method of detecting a target polynucleotide in a sample, i.e., a polynucleotide having a sequence of a polynucleotide of former claim 12.

The rejection is not supported because it ignores the limitation that the claims are directed to detecting specific **target polynucleotides**, disclosed in the specification. One cannot practice the recited methods of detecting a target polynucleotide if one does not know the identity of that target polynucleotide, or even whether that target polynucleotide exists. Without knowledge of a target polynucleotide, one would not have any conception of practicing a method of detecting it, one would not have any motivation to attempt to detect it, and one would certainly not have the ability to detect it. By focusing on the alleged obviousness of the probes used in the claimed methods, the Examiner has ignored the fact that the claimed methods require detection of the recited **target polynucleotides**. Since there is no suggestion or teaching in the art to detect the recited target polynucleotides, one would not have been guided to practice the claimed methods.

Applicants note that the dictionary defines "specific" as "restricted to a particular individual, situation, relation, or effect." (Attachment No. 1; Merriam-Webster's Collegiate Dictionary; Merriam-Webster OnLine: http://www.m-w.com.) Hence, the phrase "specifically hybridizes" indicates that the

probes of claims 14-16, as currently amended, bind only to the polynucleotides of claim 12 and thus would not by definition bind to any oligomer, if any, taught by Hillier et al. It is well known and an inherent requirement of the method that the primers used in PCR amplification must specifically hybridize to the target polynucleotide.

Furthermore, Hillier et al. do not teach a degenerate probe suitable for use to detect the polynucleotides of claims 14-16, as currently amended. Though one of skill in the art may well attempt to design degenerate probes from especially those which would specifically hybridize to the polynucleotides of claims 14-16, as currently amended, they are not suggested from the Hillier et al. document. Only through ***hindsight***, could one detect the novel, full-length, 1135 nucleotide human S-adenosyl-L-methionine methyltransferase from a sample using the Hillier 463 nucleotide cDNA fragment.

2. Obvious "to try"

No matter how obvious it might have been to try to detect the specific full length sequence claimed in claims 14-16, even assuming, *arguendo*, that it might be obvious to try to detect an unknown full-length sequence based on the existence of a gene encoding a human methyltransferase in the prior art, obvious to try does not support a rejection under 35 U.S.C. § 103.

> ". . . [o]bvious to try" has long been held not to constitute obviousness. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *In re Deuel*, 34 USPQ2d 1210 (CAFC 1995).

The Examiner alleges that the method of detecting a polynucleotide of SEQ ID NO:2 is obvious because a human cDNA fragment encoding a methyltransferase (e.g., the cited Hillier et al. reference) was identified. However, it is respectfully pointed out that the methyltransferase fragment was NOT identified as being a part of Applicants' claimed sequence of SEQ ID NO:2, which had not yet been elucidated. Accordingly, at most the combined cited prior art suggest that is would be obvious to try to clone a full-length sequence of the human S-adenosyl-L-methionine methyltransferase gene. Yet, as

stated in *In re O'Farrell* ". . . [o]bvious to try" is not a standard for obviousness under 35 U.S.C. § 103.

Applicants respectfully submit that the rejection fails to state a proper *prima facie* case of obviousness, and that the rejection should, therefore, be withdrawn.

C. Summary

The combined cited prior art does not teach or suggest the detection of the target polynucleotides recited in claims 14-16. Since this reference does not teach or suggest **all** of the claim limitations, the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103 have not been met.

For at least the above reasons, this rejection should be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections and rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: August 18, 2003

Gina C. Nellesen
Reg. No. 52,062
Direct Dial Telephone: (650) 843-7342

Date: August 18, 2003

James M. Verna, Ph.D.
Reg. No. 33,287
Direct Dial Telephone: (650) 845-5415

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

Enclosures:

1. Merriam-Webster's Collegiate Dictionary; Merriam- Webster OnLine: http://www.m-w.com.

2. Lodish, Harvey F. 1986 Molecular Cell Biology, Fourth Edition W. H. FREEMAN.

3. Brenner et al., Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998).

4. John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999).

5. Lashkari, et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, (August 1997) Proc. Nat. Acad. Sci. U.S.A. 94:8945-8947.

6. Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999).

7. Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

8. John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107:681-685 (1999).

9. Email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding.